



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov



APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/811,793	03/29/2004	John R. Plachetka	7569/80993	2542
7590	08/08/2005			
Michael A Sanzo Fitch Even Tabin & Flannery 1801 K Street NW Suite 401L Washington, DC 20006-1201			EXAMINER CHOI, FRANK I	
			ART UNIT 1616	PAPER NUMBER
DATE MAILED: 08/08/2005				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/811,793	PLACHETKA ET AL.
	Examiner	Art Unit
	Frank I. Choi	1616

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 8/20/2004 (Protest), 10/19/2004(Comments).
 2a) This action is FINAL. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 5-29 and 34-41 is/are pending in the application.
 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 5-29 and 34-41 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on 29 March 2004 is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____. |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08),
Paper No(s)/Mail Date <u>20040415, 20040513, 20040805, 20040820</u> | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| | 6) <input type="checkbox"/> Other: _____. |

DETAILED ACTION

Applicant is reminded of the continuing obligation under 37 CFR 1.178(b), to timely apprise the Office of any prior or concurrent proceeding in which Patent No. 6,479,551 is or was involved. These proceedings would include interferences, reissues, reexaminations, and litigation.

Applicant is further reminded of the continuing obligation under 37 CFR 1.56, to timely apprise the Office of any information which is material to patentability of the claims under consideration in this reissue application.

These obligations rest with each individual associated with the filing and prosecution of this application for reissue. See also MPEP §§ 1404, 1442.01 and 1442.04.

Protest

Examiner has duly considered the protest filed under 37 CFR 1.291(a) on August 20, 2004 and Applicant's Comments in Response to Protest filed on October 19, 2004 and responds as follows:

35 U.S.C. 112 Arguments

Examiner concurs with Applicant's comments to the extent that the limitation "coordinate" as used in claims 6, 7 and 9 is not indefinite.

35 U.S.C. 103 Arguments

Examiner concurs with Applicant's comments relative to the rejection of claim 5 over Saadah in view of Gergely or, alternatively, over Sims in view of Saadah, in further view of Gergely, to the extent that there is no motivation to combine Saadah or Sims with Gergely in that there is no basis for concluding that the formulation in Gergely would inhibit the reduction of

Art Unit: 1616

potency of the metoclopramide as defined in the Specification. Examiner notes that Gergely inhibits the interaction between the alkali sensitive drug, for example acetylsalicylic acid and the alkaline compound by combining the alkaline compound with citric acid and allowing a partial reaction and conversion to citrate salts and then adding more citric acid to coat (Column 11, lines 33-68). As such, one of ordinary skill in the art would be motivated to mix metoclopramide with an acid, which may result in reduced potency, as opposed to keeping the acid and metoclopramide separate.

Examiner concurs with Applicant's comments relative to the rejection of claims 6, 7, 9-18 over Moore in view of Greiff, in further view of Gergely and Saadah, to the extent that there is no motivation to combine Gergely with the other references and that Moore is not prior art relative to claims 10,12,18. With respect to Claim 9, contrary to the Protest, ergotamine tartrate which is recited in Saadah is a 5HT agonist vasoactive agent.

With respect to claims 6,7,9,11,13,14-17, contrary to Applicant's comments, Moore does constitute prior art. Claims 6, 7, 9, 17 recite the use of analgesics, claims 14-16 recite the use of drugs, claim 11 recites specific NSAIDs and claim 13 recites NSAIDs which are formulated to be long acting for which there is no written description in the priority applications. The written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991) (While acknowledging that some of its cases concerning the written description requirement and the enablement requirement are confusing, the Federal Circuit reaffirmed that under 35 U.S.C. 112, first paragraph, the written description requirement is separate and distinct from the enablement

requirement and gave an example thereof.). An invention may be described without the disclosure being enabling (e.g., a chemical compound for which there is no disclosed or apparent method of making), and a disclosure could be enabling without describing the invention (e.g., a specification describing a method of making and using a paint composition made of functionally defined ingredients within broad ranges would be enabling for formulations falling within the description but would not describe any specific formulation). As such, with respect to claims 6, 7, 9, 14-17, although use of analgesics, drugs and the newly disclosed specific NSAIDs may have been enabled by the limitation “NSAID” in the priority application, there was no written description of the use of said specified NSAIDs or the use of analgesics or drugs in general. With respect to claim 13, “long acting NSAIDs” cannot be read to include “formulated to be long acting” as the priority application clearly recites the use of NSAIDs which are inherently long acting, i.e. do not require preparation in a formulation to be long acting. Even if “long acting NSAIDs” would enable one of ordinary skill in the art to formulate NSAIDs to be long acting, there is no written description of the same. Thus, Claims 6, 7, 9, 11 and 13-17 are not entitled to the priority date of November 10, 1997 or November 12, 1996 and have an effective date of March 3, 2000.

Although Moore and Greiff do disclose sequential administration of an metoclopramide prior to administration of an NSAID, the limitation “coordinated dosage form” or “dosage form is coordinated” requires that metoclopramide and the NSAID be contained together in the same dosage form but formulated to release metoclopramide so that it reaches therapeutic levels faster than the NSAID as defined in the Specification. As such, the teachings of Moore and Greiff combined with the other references alone are insufficient to suggest a coordinated dosage form,

i.e. there is no teaching in the references cited from which one of ordinary skill in the art could modify the teachings of sequential administration to prepare a single dosage form which in effect results in sequential administration of metoclopramide and the NSAID.

With respect to the rejection of claim 8 over Moore and Greiff, in view of Saadah and Gergely, in further view of Seiyaku, contrary to Applicant's comments, Moore and Seiyaku do constitute prior art in that claim 8 recites the use of analgesics in general (See discussion above). However, as indicated above, there is no motivation to combine Gergely with the other references. Further, notwithstanding Gergely, the combined teachings of Moore, Greiff, Saadah and Seiyaku would not suggest to one of ordinary skill in the art the claimed invention. The Protest argues that it would have been obvious to replace the sucralfate of Seiyaku with metoclopramide for the purpose of protecting a patient's digestive system from irritation due to the analgesic, however, the Protest does not cite to any teaching which discloses that metoclopramide has this function. Even if metoclopramide had this function, replacing sucralfate with metoclopramide would not result in the claimed invention. The sucralfate in Seiyaku is contained in a delayed release portion of the dosage form whereas the drug is contained in the immediate releasing portion of the dosage form (Pg. 3). As indicated above, the limitation "coordinated" requires that the metoclopramide be released first.

With respect to the rejection of claims 13, 19, 25, 29 and 41 over Chen in view of the discussion of Claims 10, 14, 22, 34 and 35, respectively, contrary to Applicant's comments, Chen is prior art with respect to claims 13, 19, 29 and 41 for the reasons indicated above relative to claim 13, with respect to claim 25 because the priority applications lack written description of the limitation "non-acidic analgesic" and with respect to claim 29 because priority applications

Art Unit: 1616

lack written description of the limitation “analgesics” (See discussion above). However, assuming that it would have been obvious to one of ordinary skill in the art to combine the teaching of Chen with the references discussed in claims 10, 14, 22, 34 and 35, respectively, the combination would not suggested the claimed invention. As indicated above, with respect to claims 10, 14, there is no motivation to combine Gergely with the other references and the combination of Moore and Greiff with the other references alone do not suggest a coordinated dosage form. Claims 22, 34, 35 relative to Chen are discussed below.

With respect to the rejection of claims 22, 23, 24 over Greiff and Moore, in view of Poyser, contrary to Applicant’s comment, Moore is prior art as claim 22 recites non-acidic analgesics in general, whereas, as indicated above, the priority applications only recited the use of NSAIDs. However, as indicated above, the combination of Greiff and Moore and the other references alone do not disclose or suggested a coordinated dosage form. Regardless of whether Poyser would have suggested to one of ordinary skill in the art to use a non-acidic analgesic, to formulate the combination in a tablet or to not include a 5HT agonist vasoactive agent, Poyser does not disclose a coordinated dosage form. Examiner notes that paracetamol is actually slightly acidic in water but has a pKa falling within the definition of “non-acidic analgesic” set forth in the Specification (Column 2, lines 16-18) (See discussion below). Similarly, with respect to claims 25 and 29, since Chen does not disclose a coordinated dosage form either, the combination of said references does not suggest the claimed invention regardless of whether Chen discloses the formulation of long-acting NSAIDs or analgesics.

With respect to the rejection of claim 34 over Saadah and Gergely, in view of Seiyaku, contrary to Applicant’s comments, Seiyaku is prior art since the use of analgesics in general is

Art Unit: 1616

recited (see discussion above). However, regardless of whether Seiyaku would suggest to one of ordinary skill in the art to make a multilayered tablet, as indicated above, there is no motivation to combine Gergely with the other references. Similarly, regardless of whether Chen discloses NSAIDs which are long acting or formulated to be long acting relative to claim 41, there is no motivation to combine Gergely with the other references.

With respect to the rejection of claims 35-40 over Gergely and Saadah, in view of Greiff and Moore, contrary to Applicant's comment, Moore is prior art with respect to claims 35-37, 39 since the use of analgesics in general is recited in claims 35-37 and the use of specified NSAIDs not disclosed in the priority applications are recited in claim 39 (see discussion above). However, regardless of whether Saadah discloses the use of naproxen relative to claims 38-40, there is no motivation to combine Gergely with the other references. Also, as indicated above, the combined teachings of Greiff and Moore with the other references alone are insufficient to suggest a coordinated dosage form. Further, contrary to the Protest, with respect to claim 36, Gergely does not disclose a multilayer tablet at column 11, lines 34-38; the acetylsalicylic acid is uniformly mixed with the effervescent base and other additives (Column 11, lines 67, 68). With respect to claim 37, as indicated above, ergotamine tartrate which is disclosed in Saadah is a 5-HT agonist vasoactive agent. Similarly, regardless of whether Chen discloses NSAIDs which are long acting or formulated to be long acting relative to claim 41, there is no motivation to combine Gergely with the other references.

Specification

The amendment filed 3/29/2004 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall

introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The amendment contains additional description of Poyser et al. (US Pat. 4,380,540) relating to paracetamol or paracetamol DC and that formulations containing aspirin undergo unacceptable degradation in a matter of two to three weeks at ambient temperatures. The disclosure of Poyser et al. was not incorporated by reference, as such, the additional material relative to paracetamol and paracetamol DC constitutes new matter. Further, the Specification as originally filed does not state that formulations containing aspirin undergo unacceptable degradation, the Specification as originally filed specifically indicated that formulation in Poyser et al. in which aspirin is intermixed with metoclopramide went unacceptable degradation. As such, the amendment relative to formulations containing aspirin constitutes new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-7, 9-29, 35-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for acid-base storage stabilized dosage forms in which metoclopramide and/or analgesic are barrier coated or are in separate layers of a multilayered dosage form separated by intermediate layer containing no metoclopramide and analgesic and coordinated dosage forms in which the analgesic or matrix containing the same is barrier coated or formulated to delay release and the metoclopramide is immediately releasable either from the

same matrix or a separate layer does not reasonably provide enablement for undisclosed acid-base stabilized dosage form or undisclosed coordinated dosage forms. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The nature of the invention:

The invention is directed to a pharmaceutical composition in unit dosage form comprising metoclopramide and analgesic in acid-base storage stabilized form and/or metoclopramide and analgesic in coordinated dosage form.

The state of the prior art and the predictability or lack thereof in the art:

The prior art of record does not appear to disclose other acid-base storage stabilized forms other than forming a barrier coating or addition of the active agents into separate layers of a multi-layered dosage form or the separate coordinated delivery of metaclopramide and analgesic in a single dosage form.

The amount of direction or guidance present and the presence or absence of working examples:

The Specification only discloses the use of barrier coatings and separate layers.

The breadth of the claims and the quantity of experimentation needed:

The claims are broad in that the terms "acid-base storage stabilized form" and "coordinated" define an intended effect but not how the intended effect is supposed to be arrived at other than through the use of barrier coatings and separate layers. As such, it appears that one of ordinary skill in the art would be required to do undue administration to determine other acid-base storage stabilized forms and how to sequentially deliver the active agents when the active

Art Unit: 1616

agents are in a single dosage form other than the use of barrier coatings or separate layers.

Further, if the metoclopramide is barrier coated and the analgesic is barrier coated or not, as indicated in claim 36, it appears that one of ordinary skill in the art would be required to do undue experimentation in order to determine what formulations of barrier coatings would result in coordinated delivery of metoclopramide and the analgesic.

Claims 11,20,39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's claims include NSAIDs. The Specification defines NSAIDS as including acetaminophen. However, acetaminophen, although having a high pKa of 9.51, is a weakly acidic drug, having in a saturated solution a pH of 5.3-6.5, which lacks the anti-inflammatory properties of aspirin. See Remington's (17th Ed. 1985), pg. 1111. As such, acetaminophen cannot be claimed to be an NSAID. In light of the above, the scope of the invention is unclear. See MPEP Sections 2171, 2172.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 6-9, 11, 13-17, 19, 20, 22-29, 34-37, 39, 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hsiao et al. (U.S. Pat. 5,885,616) in view of Poyser et al. (U.S. Pat. 4,325,971), Tfelt-Hansen et al. (Lancet 1995; 346:923-926), Pradalier et al. (Headache 28: 550-

Art Unit: 1616

557, 1988), Beubler, Mandell, Ferrari et al. and Ross-Lee et al. (Eur J. Clin Pharmacol (1983) 24: 777-785).

Hsiao et al. teaches multilayered dosage forms where the outer layer is immediately released whereas the inner layer is sustained release which are separated from each other by a polymer layer in which aspirin and metoclopramide are taught as a suitable drugs (Columns 2, 3, Column 5, lines 15-49).

Poyser et al. teach the combination of analgesics, such as coated paracetamol, paracetamol or acetylsalicylic acid and the like in single dosage forms for the treatment of migraine and that metoclopramide potentiates the effects of analgesics (See entire document).

Tfelt-Hansen et al. discloses that the most commonly used drug for treatment of migraine is aspirin but that during migraine attacks aspirin absorption is delayed due to gastric stasis (Pg. 923). It is disclosed that metoclopramide is combined with aspirin to return the absorption of aspirin to normal during migraine attacks, enhance the effect of aspirin and combat nausea and vomiting (Pg. 923). It is disclosed that sumatriptan is expensive and has adverse effects (Pg. 925).

Pradalier et al. discloses that NSAIDs, such as aspirin and naproxen, are effective in treating migraine (See entire document).

Beubler disclose that aspirin, acetaminophen, ibuprofen, naproxen and metoclopramide are used to treat migraine and that the side effects of ergotamine and dihydroergotamine are troublesome (Abstract).

Mandell teaches that selective cyclooxygenase-2 inhibitors, such as celecoxib, are as effective as other NSAIDs, but cause less GI ulceration and bleeding (Abstract).

Ferrari et al. disclose that use of serotonergic vasoconstrictors such as sumatriptan and ergotamine although effective can result in recurrence of migraine or rebound headache (Abstract).

Ross-Lee et al. teach that pretreatment with metoclopramide overcomes the reduced gastro-intestinal motility associated with migraine and results in faster delivery of aspirin (See entire document).

The difference between the prior art and the claimed invention is that the prior art does not expressly disclose the combination of metoclopramide and naproxen in acid-base storage stabilized dosage form, the combination of metoclopramide and analgesic, drug or non-acidic analgesic in coordinated dosage forms, the combination of metoclopramide and analgesic in an acid-base storage stabilized dosage form in which said metoclopramide and said analgesic are each in separate layers of a multilayer tablet, or the combination of metoclopramide and analgesic where the dosage form is an acid-base storage stabilized and coordinated dosage form. However, the prior art amply suggests the same as multi-delivery and multi-layered dosage forms, the combination of metaclopramide and analgesics, such as NSAIDs, are disclosed in the prior art. Further, the prior art discloses pretreating with metaclopramide when administering analgesics, such as NSAIDs, for treatment of migraine. As such, it would have been well within the skill of and one of ordinary skill in the art would have been motivated to modify the prior art as above with the expectation that analgesics, such as NSAIDs, as a class would be effective in treating migraine and that metoclopramide would increase the effectiveness and absorption of the analgesic. Further, one of ordinary skill in the art would have been motivated to formulate a dosage form wherein metoclopramide is in the immediate release layer and the analgesic is in the

sustained release layer as it is known that pretreatment with metoclopramide overcomes the reduced gut motility associated with migraine, with the expectation that sustained release of the analgesic would increase effective treatment time and require less dosing, that the separation of the metoclopramide and analgesic into different layers would prevent any adverse interaction and that a single dosage form would be more convenient to administrate than separate dosages of different drugs. Finally, although an acid-base storage stabilized form is not explicitly disclosed, Hsaio discloses a polymer layer between the immediately releasing layer and the sustained release layer, as such, the metoclopramide contained in the immediately releasing layer and the analgesic in the sustained release layer will not interact during storage.

Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention has been collectively taught by the combined teachings of the references.

Claims 6-29, 34-39, 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al. (US Pat. 4,938,967) in view of Raff (US Pat. 3, 279,998), Poyser et al. (U.S. Pat. 4,325,971), Tfelt-Hansen et al. (Lancet 1995; 346:923-926), Pradalier et al. (Headache 28: 550-557, 1988), Beubler, Mandell, Ferrari et al. and Ross-Lee et al. (Eur J. Clin Pharmacol (1983) 24: 777-785).

Newton et al. teaches a tablet dosage form which combines an immediate release component and a sustained release component in which metoclopramide is taught as a suitable drug (Column 7, 10-24, Column 8, lines 18-31, Column 13, line 2)

Raff et al. discloses a sustained release tablet containing an immediate release layer and a sustained release layer (Column 4, lines 21-38).

Poyer et al., Tfelt-Hansen et al., Pradalier et al., Beubler, Mandell, Ferrari et al. and Ross-Lee et al. are cited here for the same reasons as above and are incorporated herein to avoid repetition.

The difference between the prior art and the claimed invention is that the prior art does not expressly disclose the combination of metoclopramide and naproxen in acid-base storage stabilized dosage form, the combination of metoclopramide and analgesic, drug or non-acidic analgesic in coordinated dosage forms, the combination of metoclopramide and analgesic in an acid-base storage stabilized dosage form in which said metoclopramide and said analgesic are each in separate layers of a multilayer tablet, or the combination of metoclopramide and analgesic where the dosage form is an acid-base storage stabilized and coordinated dosage form. However, the prior art amply suggests the same as multi-delivery and multi-layered dosage forms, the combination of metaclopramide and analgesics, such as NSAIDs, are disclosed in the prior art. Further, the prior art discloses pretreating with metaclopramide when administering analgesics, such as NSAIDs, for treatment of migraine. As such, it would have been well within the skill of and one of ordinary skill in the art would have been motivated to modify the prior art as above with the expectation that analgesics, such as NSAIDs, as a class would be effective in treating migraine and that metoclopramide would increase the effectiveness and absorption of the analgesic. Further, one of ordinary skill in the art would have been motivated to formulate a dosage form wherein metoclopramide is in the immediate release layer and the analgesic is in the sustained release layer as it is known that pretreatment with metoclopramide overcomes the reduced gut motility associated with migraine, with the expectation that sustained release of the analgesic would increase effective treatment time and require less dosing, that the separation of

the metoclopramide and analgesic into different layers would prevent any adverse interaction and that a single dosage form would be more convenient to administrate than separate dosages of different drugs. Finally, although an acid-base storage stabilized form is not explicitly disclosed, Poyser et al. discloses coated paracetamol, as such, the paracetamol in the coated paracetamol willl not interact with the metoclopramide during storage.

Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention has been collectively taught by the combined teachings of the references.

Claims 5-7, 9-29, 35-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shah et al. (US Pat. 6,126,969) in view of Poyser et al. (U.S. Pat. 4,325,971), Tfelt-Hansen et al. (Lancet 1995; 346:923-926), Pradalier et al. (Headache 28: 550-557, 1988), Beubler, Mandell, Ferrari et al. and Ross-Lee et al. (Eur J. Clin Pharmacol (1983) 24: 777-785).

Shah et al. discloses a tablet or capsule containing an active pharmaceutical principle which is coated to provide controlled sustained release of the active ingredient which is combined with an uncoated pharmaceutically active ingredient which can be different from the sustained-release coated pharmaceutically active ingredient and that the active ingredients can include migraine treatments, metoclopramide and anti-inflammatory drugs such as indomethacin, naproxen, ibuprofen or flurbiprofen (Column 5, lines 45-60, Column 6, lines 1, 11, 13,14, Column 7, lines 7-15).

Poyser et al., Tfelt-Hansen et al., Pradalier et al., Beubler, Mandell, Ferrari et al. and Ross-Lee et al. are cited here for the same reasons as above and are incorporated herein to avoid repetition.

Art Unit: 1616

The difference between the prior art and the claimed invention is that the prior art does not expressly disclose the combination of metoclopramide and naproxen in acid-base storage stabilized dosage form, the combination of metoclopramide and analgesic, drug or non-acidic analgesic in coordinated dosage forms, or the combination of metoclopramide and analgesic where the dosage form is an acid-base storage stabilized and coordinated dosage form.

However, the prior art amply suggests the same as multi-delivery dosage forms, the combination of metaclopramide and analgesics, such as NSAIDs, are disclosed in the prior art. Further, the prior art discloses pretreating with metaclopramide when administering analgesics, such as NSAIDs, for treatment of migraine. As such, it would have been well within the skill of and one of ordinary skill in the art would have been motivated to modify the prior art as above with the expectation that analgesics, such as NSAIDs, as a class would be effective in treating migraine and that metoclopramide would increase the effectiveness and absorption of the analgesic.

Further, one of ordinary skill in the art would have been motivated to formulate a dosage form wherein metoclopramide is immediate released and the analgesic coated by a sustained release coating, as it is known that pretreatment with metoclopramide overcomes the reduced gut motility associated with migraine, with the expectation that sustained release of the analgesic would increase effective treatment time and require less dosing, that the separation of the metoclopramide and analgesic by the coating of the analgesic would prevent any adverse interaction and that a single dosage form would be more convenient to administrate than separate dosages of different drugs. Finally, although an acid-base storage stabilized form is not explicitly disclosed, the formulation of Shah et al. would result in the analgesic being coated and thus would not interact with the uncoated metoclopramide during storage.

Art Unit: 1616

Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention has been collectively taught by the combined teachings of the references.

Conclusion

A facsimile center has been established in Technology Center 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier number for accessing the facsimile machine is 571-273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Choi whose telephone number is (571)272-0610. Examiner maintains a flexible schedule. However, Examiner may generally be reached Monday-Friday, 8:00 am – 5:30 pm (EST), except the first Friday of the each biweek which is Examiner's normally scheduled day off.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Mr. Gary Kunz, can be reached at 571-272-0887. Additionally, Technology Center 1600's Receptionist and Customer Service can be reached at (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

FIC

August 4, 2005



Altair My
Altair Primary Examiner
Primary 1616
AU.16